10/473,578

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 487/04, 471/04, 207/22 C07D 211/04 — A1

(11) International Publication Number: WO 92/10499

(43) International Publication Date: 25 June 1992 (25.06.92)

(21) International Application Number: PCT/GB91/02209

(22) International Filing Date: 12 December 1991 (12.12.91)

(30) Priority data:
9026926.7 12 December 1990 (12.12.90) GB

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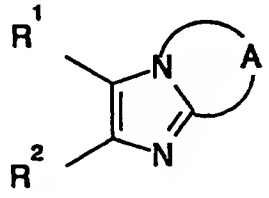
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL PROCESS



(1)

(57) Abstract

A process for preparing a compound of formula (1) is described wherein R^1 and R^2 are independently optionally substituted pyridinyl, or optionally substituted phenyl and A is propane-1,3-diyl or butane-1,4-diyl optionally substituted by one or two C_{1-2}alkyl groups.

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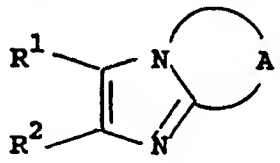
NOVEL PROCESS

The present invention relates to a novel process for preparing fused imidazole derivatives and intermediates used in the process.

Various fused imidazole derivatives have been disclosed as medicaments in US-A-4719218, EP-A-231622, EP-A-306300 and EP-A-364204. An advantageous process has now been discovered for the synthesis of such derivatives.

Accordingly, the present invention provides a process for preparing a compound of the formula (1) :



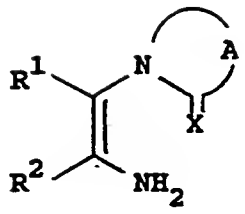
(1)

wherein

R^1 and R^2 are independently optionally substituted pyridinyl, or optionally substituted phenyl, and

A is propane-1,3-diyl or butane-1,4-diyl optionally substituted by one or two C_{1-2}alkyl groups,

which process comprises cyclising a compound of the formula (2) :



(2)

or the E-isomer thereof,

wherein X is oxygen or sulphur and R^1, R^2 and A are as hereinbefore defined.

Suitably one of R^1 and R^2 is optionally substituted pyridinyl and the other is optionally substituted phenyl.

More suitably R^1 is optionally substituted pyridinyl and R^2 is optionally substituted phenyl.

Examples of R^1 and R^2 are as disclosed in the above-noted patents and patent applications.

Suitably R^1 is pyridinyl optionally substituted by C_{1-4}alkyl.

Preferably R^1 is 4-pyridinyl optionally substituted in the 2-position by C_{1-4}alkyl.

Suitably R^2 is phenyl optionally substituted by C_{1-4}alkyl $S(O)_m$ wherein m is 0 or 1, or by halo or C_{1-4}alkoxy.

More suitably R^2 is phenyl substituted by C_{1-4}alkylthio.

Preferably R^2 is phenyl substituted in the 4-position by C_{1-4}alkylthio.

Examples of C_{1-4}alkyl in the definitions of R^1 and R^2 include methyl, ethyl, propyl and butyl.

Examples of halo include fluoro, chloro, bromo, and iodo.

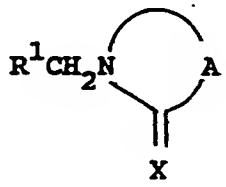
Examples of compounds of the formula (1) which can be prepared by the present process include :

6,7-dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
6,7-dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
2-(4-bromophenyl)-6,7-dihydro-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
6,7-dihydro-2-(4-ethylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
6,7-dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
6,7-dihydro-2-(4-methylthiophenyl)-3-phenyl-5H-pyrrolo[1,2-a] imidazole, or
6,7,8,9-tetrahydro-2-(4-methylthiophenyl)-3-pyridyl-5H-pyrido[1,2-a] imidazole.

Compounds of the formula (1) wherein R^2 is phenyl substituted by C_{1-4}alkylthio, e.g. 6,7-dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]-imidazole, are of particular interest. They are inhibitors of the 5-lipoxygenase pathway and also useful intermediates since they can be oxidised to their C_{1-4}alkylsulphinyl analogues.

In another aspect the present invention provides a compound of the formula (2) as hereinbefore defined.

A compound of the formula (2) can be prepared by reacting in the presence of a suitable base a compound of the formula (3) :



(3)

with a compound of the formula (4) :

$$R^2CN \qquad (4)$$

wherein R^1, R^2, X and A are as hereinbefore defined.

Examples of suitable bases include alkyl lithiums such as n-butyl lithium, potassium tert-butoxide, lithium diisopropylamide, lithium hexamethyldisilazide, sodium or potassium hydride or potassium hydroxide optionally with a phase transfer catalyst such as tetraoctylammonium bromide, or a suitable mixture thereof, e.g. n-butyl lithium and potassium tert butoxide. Conveniently a compound of the formula (3) is reacted with an excess of base, suitably 1 to 2 mole equivalents, preferably 1.0 to 1.5 mole equivalents of the base before treatment with a compound of the formula (4).

The reaction of a compound of the formula (3) and a compound of the formula (4) is suitably performed in an organic solvent such as tetrahydrofuran, dialkyl ether,

dimethylformamide, toluene, dimethylethylidene urea or tetramethylethylenediamine or a suitable mixture thereof within a temperature range of -80° to 100°C, conveniently with cooling initially and then at ambient temperature.

The compound of the formula (2) may be isolated on work-up and then cyclised to a compound of the formula (1) with a suitable base as hereinbefore described.

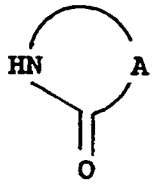
Preferably, however, the compound of the formula (2) is not isolated, but is formed <u>in situ</u> and cyclised directly to a compound of the formula (1) under the basic conditions of the reaction mixture.

In a further aspect the present invention provides a compound of the formula (3) as hereinbefore defined.

A compound of the formula (3) is suitably prepared by reacting in the presence of a base a compound of the formula (5) :

$$R^1CH_2L \qquad (5)$$

or an acid addition salt thereof, wherein R^1 is as hereinbefore defined and L is a leaving group, with a compound of the formula (6) :



(6)

wherein A is as hereinbefore defined,

and thereafter if desired converting a compound of the formula (3) wherein X is oxygen to the corresponding compound wherein X is sulphur.

Examples of bases include potassium hydroxide potassium carbonate, sodium hydride, sodium hydroxide or lithium diisopropylamide. Suitably L is halo such as bromo or chloro, tosylate or mesylate. The reaction is suitably performed in a solvent such as tetrahydrofuran, dimethylformamide, tert-butylmethylether, dichloromethane, toluene, or diethylether, or a mixture thereof, optionally in the presence of water in appropriate cases, for example when using solid potassium hydroxide together with a phase transfer catalyst as the base. The reaction is conveniently performed at ambient or elevated temperature e.g. 30° to 100°C preferably below 60°C. Preferably an aqueous solution of an acid addition salt of a compound of the formula (5) is gradually added to a solution of a compound of the formula (6) and the base.

A compound of the formula (3) wherein X is oxygen can suitably be converted to the corresponding compound wherein X is sulphur by treatment with a reagent such as Lawesson's reagent (Org. Syn., 1984, Vol. 62, 158) or Belleau's reagent (Tet. Lett., 1983, 3815).

In a particular embodiment the present invention provides a process for preparing 6,7-dihydro-2-(4-methylthio-phenyl)3-(4-pyridinyl)-5H-pyrrolo[1,2-a]-imidazole which comprises:

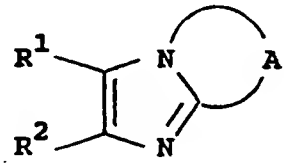
a) reacting an acid addition salt of 4-picolylchloride with a basic solution of 2-pyrrolidinone to form 1-(4-picolyl)-2-pyrrolidinone;

b) reacting in the presence of a suitable base 1-(4-picolyl)-2-pyrrolidinone with 4-methylthio-benzonitrile to form Z-1-amino-1-(4-methylthiophenyl)-2-(4-pyridyl)-2-(1-(2-oxo-pyrrolidinyl))ethene which is cyclised in situ to form the desired compound.

If desired a compound of the formula (1) wherein R^1 and/or R^2 is phenyl substituted by C_{1-4}alkylthio can be converted to the corresponding compound wherein R^1 or R^2 is phenyl substituted by C_{1-4}alkylsulphinyl by treatment with a suitable oxidising agent. Examples of such agents include sodium periodate, ceric ammonium nitrate, potassium persulphate, magnesium monoperoxyphthalate, hydrogen peroxide, bromine, N-bromosuccinimide, or sodium perborate.

It has now been discovered that surprisingly a particularly selective oxidising agent for the above-noted oxidation is nitric acid. The desired C_{1-4}alkylsulphinyl compounds can be readily obtained in the absence of undesired, over-oxidised C_{1-4}alkylsulphonyl compounds.

Thus, in a further aspect the present invention provides a process for preparing a compound of the formula (1) :



(1)

wherein one or both of R^1 and R^2 is phenyl substituted by C_{1-4}alkylsulphinyl, and the other and A

are as hereinbefore defined, which comprises reacting the corresponding C_{1-4}alkylthio substituted compound with nitric acid.

Suitably R^2 is phenyl substituted by C_{1-4}alkylsulphinyl.

A particular compound that can be prepared by this process is 6,7-dihydro-2-(4-methylsulphinylphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole.

Suitably concentrated nitric acid is added to a mixture of the C_{1-4}alkylthio compound of formula (1) in a solvent such as water or aqueous sulphuric acid or nitromethane or mixtures thereof, with cooling (e.g. 0 to 5°C) and the reaction mixture is then stirred at ambient temperature.

Example 1

6,7-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo [1,2-a] imidazole

a) To a vigorously stirred suspension of potassium hydroxide (341.0 g, 6.09 mol) and tetraethylammonium bromide (51.2 g, 0.24 mol) in tetrahydrofuran (THF) (2.0 l) was added 2-pyrrolidinone (97.2 ml, 1.28 mol) at 20°C. A thick white slurry formed and the temperature rose to 27°C within 30 minutes.

The reaction mixture was stirred mechanically for a total of 100 minutes between 20-30°C before 4-picolyl chloride hydrochloride (200.0 g, 1.22 mol) in demineralised water (120 ml) was added over 25 minutes. The temperature rose to 40°C and was not allowed to rise above this. The reaction mixture was stirred for 120 minutes after this addition and was then filtered through Celite. The reaction flask and filtered solids were washed with THF (400 ml) and the washings combined with the filtrate. Any aqueous material carried over during the filtration was separated before the organic solution was concentrated to a volume of 800 ml by atmospheric distillation of the THF. The solution was cooled to 20°C at which point 60-80 petrol (500 ml) was added. The solution was stirred for 10 minutes when a further 500 ml quantity of 60-80 petrol was added. This mixture was stirred for a further 10 minutes when a final 600 ml quantity of 60-80 petrol was added. The mixture was cooled to 5°C for 16 hours before the product was isolated by filtration, washed with 60-80 petrol (400 ml), and dried at 40°C, 100 mmHg for 24 hours. Hence 1-(4-picolyl)-2-pyrrolidinone 186.0 g (86%) was obtained as a pale brown granular crystalline solid; m.p. 82-84°C; M^+, 176.0947. $C_{10}H_{12}N_2O$ requires 176.0950;

m/z 176, (M^+), 147 ($M^+ - C_2H_5$), 119 (147-CO) and 93 (119 - HCN); ν maximum (KBr) 2950, 1690 (C=O), 1600, 1450, 1420, 1300 and 1280 cm^{-1}; δH(270 MHz, $CDCl_3$) 1.85 (2H, m, $-CH_2CH_2CH_2-$), 2.20 (2H, t, $-CH_2C(O)$, 3.10 (2H, t, $-CH_2CH_2NRR^1$), 4.25 (2H, s, $PyCH_2-$), 6.95 (2H, m, Ar(3,5)) and 8.30 (2H, m, Ar(2,6).

b) To a solution of 1-(4-picolyl)-2-pyrrolidinone (20.0 g, 0.114 mol) in dry THF (260 ml) was added n-butyllithium (50.0 ml of a 2.5 M solution in hexane 0.125 mol) at 0 to -10°C. The addition required 10 minutes. Potassium tert-butoxide (12.7 g, 0.114 mol) in THF (65 ml) was then added at 0 to -10°C over 5 minutes and the resultant golden yellow suspension stirred for 10 minutes. At this point 4-methylthiobenzonitrile (18.6 g, 0.125 mol) in THF (31 ml) was added over 5 minutes at 0° to -10°C. When the addition was complete the reaction mixture was allowed to warm to ambient temperature over 30 minutes and was maintained at this temperature for 30 minutes. After this period the reaction mixture was heated under reflux for 120 minutes and then cooled to 30°C before demineralised water (80 ml) was added. The resultant mobile solution was stirred for 30 minutes and the aqueous layer then allowed 30 minutes to separate before it was removed.

The solvent was exchanged with ethyl acetate via a put and take distillation where 140 ml solvent was removed and then replaced with 140 ml ethyl acetate. This process was continued until the base temperature reached 77°C. A further 45 ml ethyl acetate was added and the solution cooled to 50°C before 60-80 petrol (87 ml) was added. The product crystallised on cooling to room temperature and after stirring for 3 hours the suspension was cooled to 0-5°C and stirred for a further

2 hours. The product was then isolated by filtration, washed with 60-80 petrol (40 ml) and then dried at 40°C, 100 mmHg for 24 hours. Hence 6,7-dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo [1,2-a] imidazole was obtained as a pale yellow crystalline solid; 17.6 g, 50%; m.p. 172°C; δH (270MHz, CDCl3) 2.50 (3H, S, -SMe), 2.70 (2H, m, $-CH_2\underline{CH_2}$, CH_2-) 3.00 (2H, t, $-\underline{CH_2}CH_2CH_2NRR^1$), 4.05 (2H, t, $-CH_2CH_2\underline{CH_2}NRR^1$), 7.20 (2H, m, MeS Ar), 7.30 (2H,m, 3,5-Py), 7.50 (2H, m, Me S Ar) and 8.60 (2H, m, 2,6-Py).

Example 2

6,7-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo [1,2-a] imidazole

a) To a solution of 1-(4-picolyl)-2-pyrrolidinone (2.01 g, 11.4 mmol) in THF (285 ml) was added n-butyllithium (8.70 ml of a 2.5M solution in hexane, 21.7 mmol) at -70°C. The resultant yellow suspension was stirred for 90 minutes between -30 to -70°C before 4-methylthiobenzonitrile (2.72 g, 18.3 mmol) in THF (40 ml) was added at -65°C. The reaction mixture was stirred with warming to room temperature over 15 minutes and was then stirred for a further 21 hours. After this time ammonia (720µl of a 35% w/w aqueous solution) was added which caused the reaction mixture to change from blood red to yellow in colour. This solution was stirred for 30 minutes before the solvent was removed in vacuo and the residue chromatographed on silica gel using ethyl acetate: triethylamine - 96:4 as eluant. Hence Z-1-amino-1-(4-methylthiophenyl)-2-(4-pyridyl)-2-{1-(2-oxo-pyrrolidinyl)}ethene (1.2 g, 32%) was obtained as a free flowing yellow powder, m.p.

220-222°C (from ethyl acetate) M^+ 325.1271. $C_{18}H_{19}N_3OS$ requires 325.1249. ν maximum (nujol mull) 3500-3300 (N-H), 1669 (C-O), 1632 (C-C) and 1566 cm^{-1}; δH (270 MHz, d6-DMSO) 2.15 (2H, m, $-CH_2\underline{CH_2}CH_2-$), 2.35 (2H, t, $-\underline{CH_2}CH_2CH_2C(O)-$), 2.50 (3H, s, -S<u>Me</u>), 3.50 (2H, t, $-CH_2CH_2\underline{CH_2}C(O)-$), 5.70 (2H, s, $-NH_2$), 6.50 (2H, m, 3,5-Py), 7.25 (4H, m, MeS <u>Ar</u>) and 8.05 (2H, m, 2,6-Py); m/z 325(M^+), 308 ($M-NH_3$), 268 ($M-C_3H_5O$) and 150 (C_8H_8NS).

b) To a suspension of Z-1-amino-1-(4-methylthiophenyl)-2-(4-pyridyl)-2-{1-(2-pyrrolidinoyl)}ethene (114 mg, 0.351 mmol) in THF (8.8 ml) was added n-butyllithium (249 µl of a 2.5 M solution in hexane, 0.491 mmol) at -40°C. The resultant dark red solution was allowed to warm to room temperature over 30 minutes and was then stirred at this temperature for 19 hours. After this time the colour changed to light yellow. At this point the reaction mixture was assayed by HPLC and found to contain the title compound 88 mg, 82%.

<u>Example 3</u>

<u>2-(4-Fluorophenyl)-6,7-dihydro-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole</u>

To a solution of 1-(4-picolyl)-2-pyrrolidinone (56 mg, 0.318 mmol) in dry THF (8 ml) was added n-butyllithium (472 µl of a 1.0 M solution in hexane, 0.477 mmol) at -80°C. The resultant cloudy bright yellow solution was stirred between -50 to -80°C for 50 minutes before p-fluorobenzonitrile (61 mg, 0.807 mmol) was added in THF (3 ml) at -80°C. The reaction mixture was then allowed to warm to room temperature when it became dark red. It was stirred for

18 hours before the solvent was removed in vacuo and the residue chromatographed on silica gel using ethyl acetate:methanol - 4:1 as eluant. Hence the title compound was obtained (7 mg, 7%) which had identical spectroscopic properties to an authentic sample (see Example 15 of EP-A-231622).

Example 4

2-(4-Bromophenyl)-6,7-dihydro-3-(4-pyridinyl)-5H-pyrrolo-[1,2-a]imidazole

To a solution of 1-(4-picolyl)-2-pyrrolidinone (2.66 g, 15.1 mmol) in dry THF (76 ml) was added n-butyllithium (7.26 ml of a 2.5 M solution in hexane, 18.1 mmol) at -40°C. A solution of potassium tert butoxide (1.69 g, 15.1 mmol) in THF (8.5 ml) was then added and the resultant golden yellow suspension stirred at -40°C for 10 minutes. At this point a solution of 4-bromobenzonitrile (5.50 g, 30.2 mmol) in THF (50 ml) was added at -40°C and the reaction mixture then allowed to warm to room temperature. After stirring for 18 hours the reaction mixture was concentrated to dryness and the residue chromatographed on silica gel using ethyl acetate:methanol - 5:1 as eluant. Hence the title compound was obtained as a yellow crystalline solid (0.71 g, 14%); M^+ 339.0371. $C_{17}H_{14}N_3\ ^{79}Br$ requires 339.0371 M^+ 341.0387. $C_{17}H_{14}N_3\ ^{81}Br$ requires 341.0351. δH (270 MHz, $CDCl_3$) 2.65 (2H, m, $-CH_2,CH_2CH_2-$), 3.00 (2H, t, $-CH_2CH_2CH_2NRR'$), 4.00 (2H, t, $-CH_2CH_2CH_2NRR'$), 7.25 (2H, m, 3,5-Py), 7.40 (4H, m, Br-Ar) and 8.60 (2H, m, 2,6-Py); m/z 339 (M^+), 341 (M^+) 259 (M-HBr), 310 ($M-C_2H_5$) and 312 ($M-C_2H_5$).

Example 5

6,7-Dihydro-2-(4-methylsulphinylphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole

6,7-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole (100.0 g) was added to distilled water (300 ml) and the mixture cooled to 0-5°C with rapid stirring. Concentrated nitric acid (~70% w/v) (300 ml) was added at such a rate so as to keep the reaction temperature below 25°C. Upon completion of the addition the mixture was stirred at ambient temperature for three hours during which time a clear solution was obtained.

Distilled water (300 ml) was added, mixture stirred for 2 minutes and dichloromethane (300 ml) added. Mixture stirred for 15 minutes, layers allowed to separate for 15 minutes and dichloromethane solution run off. Aqueous washed again with 300 ml of dichloromethane as above.

Dichloromethane (1000 ml) was added to the aqueous layer and the mixture rapidly stirred. Forty percent w/v sodium hydroxide solution (480 ml) was added slowly ensuring temperature did not exceed 30°C. Upon completion of the addition the mixture was stirred for 15 minutes, allowed to stand for 15 minutes and the layers separated. The aqueous layer was washed with a further 1000 ml of dichloromethane as above.

The combined dichloromethane solutions were stirred with distilled water (1000 ml) for 15 minutes, the mixture passed through Celite and allowed to stand for 15 minutes. The dichloromethane solution was run off and heated to reflux. Approximately 1000 ml of dichloro-

methane was collected by distillation. Ethyl acetate (1000 ml) was added and distillation continued. 300 ml portions of distillate were collected and 300 ml portions of ethyl acetate added to the pot until the vapour temperature reached 77°C. Distillation was continued to leave a residual volume of 1500 ml.

The mixture was allowed to cool to room temperature over 2 hours and was then cooled to 0°C over 2 hours. After stirring at 0°C for 2 hours the product was collected by filtration and washed with 300 ml portion of cold ethyl acetate. Product dried at 80°C under vacuum for 24 hours. m.p. 164-166°C.

Yields typically 80-85%.

Example 6

6,7-Dihydro-2-(4-methylthiophenyl)-3-phenyl-5H-pyrrolo[1,2-a] imidazole

a) A suspension of potassium hydroxide (32.75 g, 0.585 mol), tetrabutyl ammonium bromide (7.53 g, 0.023 mol) and 2-pyrrolidinone (10.44 g, 0.123 mol) in THF (300 ml)was stirred at room temperature for 2 hours before benzyl bromide (20.00 g, 0.117 mol) was added. On addition of benzyl bromide the temperature rose to 40°C over 15 minutes and the reaction mixture was maintained at this temperature by cooling in an ice bath. Once the temperature began to fall the ice bath was removed and the reaction mixture stirred at room temperature for 18 hours. Water (40 ml) was then added and the 2-phase system stirred for 15 minutes. After this time the lower aqueous layer was separated and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed in silica gel using ethyl acetate as

eluant. Hence 1-benzyl-2-pyrrolidinone (9.46 g, 50%) was obtained as a clear viscous oil; ν_{max}. (thin film) 2900, 1690, 1420, 1280 and 1260 cm^{-1}; δH (270MHz, $CDCl_3$) 2.00 (2H,m,$-CH_2\underline{CH_2}CH_2-$), 2.40 (2H,t $-C(O)\ \underline{CH_2}-$), 3.20 (2H,t,$RR^1N\underline{CH_2}$), 4.40 -(2H,s,$Ph\underline{CH_2}-$) and 7.2-7.4 (5H,m,Ph); m/z 175 (M+) and 91.

b) To a solution of 1-benzyl-2-pyrrolidinone (1.00 g, 5.71 mmol) in THF (25 ml) was added n-butyllithium (2.70 ml of a 2.5M solution in hexane, 6.75 mmol) at -40°C. The resultant yellow-brown mixture was stirred for 5 minutes before potassium tert-butoxide (0.687 g, 6.13 mmol) in THF (3.5 ml) was added. The colour changed to red and then back to yellow-brown. The mixture was stirred at -25°C for 15 minutes before 4-methylthio-benzonitrile (1.01 g, 6.78 mmol) in THF (20. ml) was added. The colour became dark red after approximately 30 minutes. The reaction mixture was then allowed to warm to room temperature and was stirred for 18 hours before water (3.0 ml) was added. The 2-phase system was stirred for 15 minutes before the lower aqueous layer was separated. The organic layer was concentrated in vacuo and the residue chromatographed on silica gel using ethyl acetate : triethylamine - 96:4 as eluant. Hence the title compound (0.05 g, 3%) was obtained as a solid residue; δH (270MHz) 2.40 (3H,s,-SMe), 2.55 (2H,m,$-CH_2\underline{CH_2}CH_2-$), 2.95 (2H,t), 3.85 (2H,t) and 7.00-7.40 (9H,m); m/z 306 (M+).

Example 7

6,7,8,9-Tetrahydro-2-(4-methylthiophenyl)-3-pyridyl-5H-pyrido[1,2-a] imidazole

a) A suspension of 2-piperidone (31.73 g, 0.321 mol), potassium hydroxide (85.37 g, 1.524 mol) and

tetraethylammonium bromide (12.80 g, 0.061 mol) was stirred in THF (500 ml) at room temperature for 2 hours. After this time 4-chloromethylpyridine (50.00 g, 0.305 mol) in water (30.0 ml) was added over 10 minutes. The temperature rose to 40°C and was not allowed to rise higher. The exotherm ceased after 30 minutes and the temperature was allowed to fall to room temperature. After stirring for 1 hour at room temperature further potassium hydroxide (34.15 g, 0.610 mol) was added which caused the temperature to rise to 30°C. The suspension was stirred for 18 hours at room temperature after which time it was filtered and the lower aqueous layer separated. The solution was concentrated in vacuo to leave a viscous oil which was distilled using a Kugelrohr oven, b.p. 60-80°C/0.005 mm. The distillate crystallised on standing at room temperature. Hence 1-(4-picolyl)-2-piperidone was obtained 10.00 g, 17%) m.p. 79-82°C (from ether), δH (270 MHz, $CDCl_3$) 1.90 (4H,m, $-CH_2\underline{CH_2}\underline{CH_2}CH_2-$), 2.55 (2H,m), 3.25 (2H,m), 4.7 (2H,s), 7.20 (2H,d) and 8.60 (2H,d).

b) To a solution of 1-(4-picolyl)-2-piperidone (7.00 g, 36.8 mmol) in THF (91 ml) was added n-butyllithium (16.21 ml of a 2.5M solution in hexane, 40.5 mmol) at -10 - 0°C. Potassium tert-butoxide 4.13 g, 36.9 mmol) in THF (20 ml) was added to the resultant bright yellow suspension and after stirring at -10°C for 15 minutes, 4-methylthiobenzonitrile (5.50 g, 36.9 mmol) was added in THF (10 ml). The reaction mixture became dark red and was stirred at room temperature for 18 hours. After this time, water (18 ml) was added and the 2-phase system stirred for 20 minutes before the lower aqueous layer was removed. The organic layer was concentrated to dryness and the resultant yellow solid residue dissolved in hot ethyl acetate (100 ml). The solution was filtered and hexane (18 ml) added. On cooling to 5°C, the product

crystallised and after 24 hours was filtered and dried under high vacuum. Hence the title compound was obtained as a yellow crystalline solid (6.63 g, 56%), m.p. (from ethyl acetate-hexane) 205-206°C, ν_{max}, (KBr) 2950, 1600 and 1470 cm^{-1} δH (270MHz, $CDCl_3$) 2.05 (4H,m,$-CH_2\underline{CH_2}\underline{CH_2}CH_2-$), 2.55 (2H,s,S<u>Me</u>), 3.20 (2H,m), 3.90 (2H,m), 7.20 (2H,d), 7.35 (2H,d), 7.45 (2H,d) and 8.80 (2H,d); δ_C (67.80 MHz, $CDCl_3$ 16.0, 21.0, 23.3, 25.3, 44.5, 124.5, 125.2, 127.9, 131.0, 137.6, 138.3, 139.3, 146.2 and 150.7; <u>m/z</u> 321 (M+) and 306.

<u>Example 8</u>

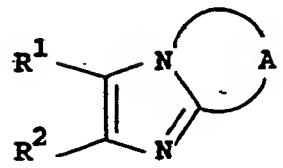
<u>6,7-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo [1,2-a] imidazole</u>

a) To a solution of 1-(4-picolyl)-2-pyrrolidinone (20.00 g, 0.114 mol) in 1,4-dioxane (260 ml) was added phosphorous pentasulphide (25.23 g, 0.114 mol) followed by further 1,4-dioxane (140 ml). The mixture was heated under reflux for 2.5 hours, cooled to room temperature and the solvent decanted from the solid residue. The solid was dissolved in ammonia solution (800 ml of a 35% aqueous solution) and water (500 ml). The solution was extracted with dichloromethane (4 x 800 ml) and the combined organic extracts concentrated to dryness. The residue was chromatographed on silica gel using ethyl acetate : hexane : triethylamine - 16:3:1 as eluant. Hence 1-(4-picolyl)-2-thiopyrrolidinone was obtained (4.66 g, 21%) as a white crystalline solid, m.p. 125-128°C (from ether); ν_{max} (KBr) 2950, 1600, 1520, 1420, 1290 and 1240 cm^{-1}, δH (270MHz, $CDCl_3$) 2.00 (2H,m, $-CH_2\underline{CH_2}CH_2-$), 3.00(2H,t), 3.70 (2H,t), 5.00 (2H,s,Py$\underline{CH_2}$-) 7.25 (2H,d,H-3 and H-5 on pyridyl ring) and 8.55 (2H,d,H-2 and H-4 on pyridyl ring); <u>m/z</u> 192 (M+) and 107.

b) To a solution of 1-(4-picolyl)-2-thiopyrrolidinone (0.500 g, 2.60 mmol) in THF (15.0 ml) was added n-butyllithium (1.15 ml of a 2.5 M solution in hexane, 2.88 mmol) at -10°C. The resultant dark red-brown solution was stirred at -10°C for 20 minutes before 4-methylthiobenzonitrile (0.580 g, 3.89 mmol) was added in 1.0 ml THF. The reaction mixture was allowed to warm to room temperature and was then heated under reflux for 2.5 hours. After this time the solution was assayed for the required product by h.p.l.c. and shown to contain the title compound (104 mg, 13%).

Claims :

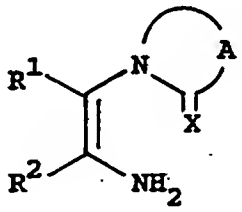
1. A process for preparing a compound of the formula (1) :



(1)

wherein
R^1 and R^2 are independently optionally substituted pyridinyl, or optionally substituted phenyl, and
A is propane-1,3-diyl or butane-1,4-diyl optionally substituted by one or two C_{1-2}alkyl groups,

which process comprises cyclising a compound of the formula (2) :



(2)

or the E-isomer thereof,

wherein X is oxygen or sulphur and R^1, R^2 and A are as hereinbefore defined.

2. A process according to claim 1 wherein one of R^1 and R^2 is optionally substituted pyridinyl and the other is optionally substituted phenyl.

3. A process according to claim 1 or 2 wherein R^1 is pyridinyl optionally substituted by C_{1-4}alkyl.

4. A process according to claim 3 wherein R^1 is 4-pyridinyl optionally substituted in the 2-position by C_{1-4}alkyl.

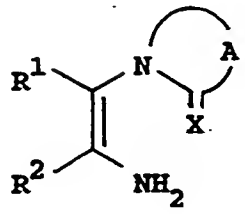
5. A process according to any one of claims 1 to 4 wherein R^2 is phenyl optionally substituted by C_{1-4}alkyl $S(O)_m$ wherein m is 0 or 1, or by halo, or C_{1-4}alkoxy.

6. A process according to any one of claims 1 to 5 wherein R^2 is phenyl substituted by C_{1-4}alkylthio.

7. A process according to claim 6 wherein R^2 is phenyl substituted in the 4-position by C_{1-4}alkylthio.

8. A process according to claim 1 wherein a compound of the formula (1) is :
6,7-dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
6,7-dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
2-(4-bromophenyl)-6,7-dihydro-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
6,7-dihydro-2-(4-ethylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
6,7-dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole,
6,7-dihydro-2-(4-methylthiophenyl)-3-phenyl-5H-pyrrolo[1,2-a] imidazole, or
6,7,8,9-tetrahydro-2-(4-methylthiophenyl)-3-pyridyl-5H-pyrido[1,2-a] imidazole

9. A compound of the formula (2) :

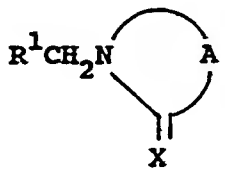


(2)

or the E-isomer thereof,

wherein R^1, R^2, X and A are as defined in any one of claims 1 to 7.

10. A process for preparing a compound of the formula (2) as defined in claim 9 which comprises reacting in the presence of a suitable base a compound of the formula (3) :



(3)

with a compound of the formula (4) :

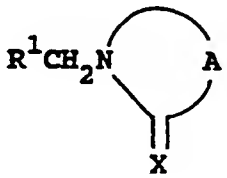
$$R^2CN \qquad (4)$$

when R^1, R^2, X and A are as hereinbefore defined.

11. A process according to claim 10 wherein the base is selected from an alkyllithium, potassium tert butoxide, lithium diisopropylamide, lithium hexamethyldisilazide, sodium or potassium hydride or potassium hydroxide, or a mixture thereof.

12. A process according to claim 10 or 11 wherein the compound of the formula (2) is not isolated but is cyclised directly to a compound of the formula (1) as defined in any one of claims 1 to 8.

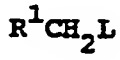
13. A compound of the formula (3) :



(3)

wherein R^1, X and A are as defined in any one of claims 1 to 7.

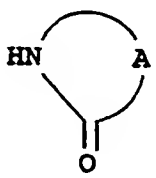
14. A process for preparing a compound of the formula (3) as defined in claim 13 which comprises reacting in the presence of a base a compound of the formula (5) :



(5)

or an acid addition salt thereof, wherein R^1 is as hereinbefore defined and L is a leaving group,

with a compound of the formula (6) :



(6)

wherein A is as hereinbefore defined,

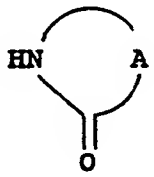
and thereafter if desired converting a compound of formula (3) wherein X is oxygen to the corresponding compound wherein X is sulphur.

15. A process for preparing a compound of the formula (1) as defined in any one of claims 1 to 8 which comprises :

a) reacting in the presence of a base a compound of the formula (5) :

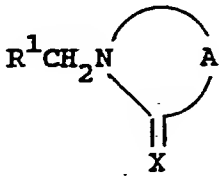
$$R^1CH_2L \qquad (5)$$

or an acid addition salt thereof, wherein R^1 is as hereinbefore defined and L is a leaving group, with a compound of the formula (6) :



(6)

where A is as hereinbefore defined, to form a compound of the formula (3) :



(3)

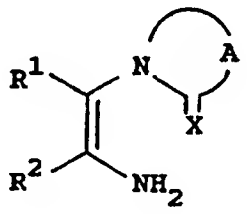
wherein X is oxygen and R^1 and A are as hereinbefore defined,

and thereafter if desired converting this to the corresponding compound wherein X is sulphur;

b) reacting in the presence of a suitable base a compound of the formula (3) as hereinbefore defined with a compound of the formula (4)

$$R^2CN \qquad (4)$$

wherein R^2 is as hereinbefore defined, to form a compound of the formula (2) :



(2)

or the E-isomer thereof,

where R^1, R^2, X and A are as hereinbefore defined; and

c) cyclising a compound of the formula (2) as hereinbefore defined.

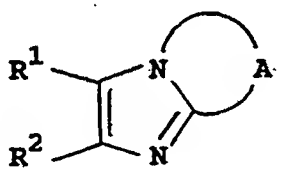
16. A process according to claim 15 which comprises:

a) reacting an acid addition salt of 4-picolylchloride with a basic solution of 2-pyrrolidinone to form 1-(4-picolyl)-2-pyrrolidinone; and

b) reacting in the presence of a suitable base 1-(4-picolyl)-2-pyrrolidinone with 4-methylthio-benzonitrile to form Z-1-amino-1-(4-methylthiophenyl)-2-(4-pyridyl)-2-{1-(2-oxo-pyrrolidinyl)}ethene which is cyclised <u>in situ</u> to form 6,7-dihydro-2-(4-methylthiophenyl)3-(4-pyridinyl)-5H-pyrrolo[1,2-a]-imidazole.

17. A process according to claim 6 or 16 or claim 1 or 2 when R^1 and/or R^2 is phenyl substituted by C_{1-4}alkylthio wherein the compound of the formula (1) is oxidised to the corresponding C_{1-4}alkylsulphinyl compound with a suitable oxidising agent.

18. A process for preparing a compound of the formula (1) :



(1)

wherein one or both of R^1 and R^2 is phenyl substituted by C_{1-4}alkylsulphinyl, and the other and A are as defined in any one of claims 1 to 7 which comprises reacting the corresponding substituted C_{1-4}alkylthio compound with nitric acid.

19. A process according to claim 18 wherein 6,7-dihydro-2-(4-methylsulphinylphenyl)3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole is produced.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/02209

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 487/04,C 07 D 471/04,C 07 D 207/22, C 07 D 211/04

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 487/00,C 07 D 471/00,C 07 D 207/00, C 07 D 211/00,A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A1, 0 364 204 (SMITHKLINE BEECHAM CO.) 18 April 1990 (18.04.90), see claims, page 7. --	1-8, 15-19
A	WO, A1, 88/01 169 (SMITHKLINE BECKMAN CO.) 25 February 1988 (25.02.88), see claims, pages 5,6. --	1-8, 15-19
A	DD, A1, 234 001 (HUMBOLDT-UNIVERSITÄT) 19 March 1986 (19.03.86), see pages 1,2. ----	9,13

* Special categories of cited documents: [14]

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 March 1992	15. 04. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MURIA TORIBIO

Form PCT/ISA/210 (second sheet) (January 1985)

ANHANG

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

to the International Search Report to the International Patent Application No.

ANNEXE

au rapport de recherche international relatif á la demande de brevet international n°

PCT/GB91/02209 SAE 54070

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés á titre indicatif et n'engagent pas la responsibilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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